REMARKS/ARGUMENTS

This amendment is filed with a Request for Continued Examination. Reconsideration and further examination are respectfully requested.

Claims 35 to 37 have been added to refer to the use of antisense oligonucleotides is that are complementary to a region of the TRPM-2 mRNA that is also complementary to SEQ ID NO: 4, 5 or 12. This amendment is supported at Page 8, lines 18-23, which defines oligonucleotides with reference to the mRNA they are complementary and defines suitable target sites with reference to Seq ID Nos. 4, 5 and 12.

Claims 38 and 39 have been added to claim the method of treatment with the combination of an antisense targeted to TRPM-2 and chemotherapy, but without the step of androgen withdrawal. These claim are supported at Page 3, lines 6-8 and 23-24 and in Example 8.

Claims 6, 8, 10, 12-17, 31 and 32 stand rejected under 35 USC § 103 as obvious over the Bruchovsky, in view of Sensibar, Kyprianou and Raghavan.

In the Official Action mailed November 14, 2006, the Examiner stated that Bruchovsky taught that "androgen withdrawal is routine treatment for prostate cancer and [provides] the suggestion to combine this with TRPM-2 gene therapy, a therapy known in the art as evidenced by the teachings of Sensibar." Applicants understood this to be an assertion that Sensibar teaches gene therapy, which it manifestly does not do. Now, in the Advisory Action, the Examiner states that Sensibar is only offered for a teaching of antisense inhibition of TRPM-2. The Examiner further asserts in the Advisory Action that "antisense inhibition of gene expression is a type of gene therapy." Applicants submit that key to this argument is any understanding in the art that the stated inhibition would be **therapeutic,** that is that it would provide any discernable benefit to a patient. This understanding is lacking. As previously noted, in the Sensibar paper, the LNCaP cells are first transfected to introduce a vector that will lead to TRPM-2 (SGP-2, clusterin) expression so that the effect of suppressing this expression can be observed. There is no teaching or suggestion in the paper of a therapeutic use of reducing TRPM-2 expression.

With respect to the previous arguments and declaration evidence concerning the expectation of success, the Examiner states that "an obviousness rejection does not require that the outcome of the experiment be known." To the extent that this is merely a statement that there does not need to be **certainty** of the outcome, Applicants would agree. However, case law consistently requires an "expectation of success." Indeed, MPEP § 2143.02 states that "Obviousness does not require absolute predictability, however, **at least some degree of predictability is required**." Here the statement relied on does not predict success, it merely states the next line of experimentation. Further, declaration evidence makes it clear that when

this statement was made, and indeed until the experiment was done, the outcome was not predictable.

> In the official action (page 3), the statement is made that:
>
> The examiner acknowledges that the effect of a decrease in TRPM-2 on apoptosis might not have been known, but this is not required by the claims, which recites that the TRPM-2 antisense inhibits expression of TRPM-2.

The Examiner reiterates this statement in the Advisory Action, but has not responded to the query made by Applicants. As stated there,

> if the effect of a decrease in TRPM-2 on apoptosis was not known, then it was not known and could not be predicted that a decrease in TRPM-2 would lead to any therapeutic benefit. Thus, there was no reasonable expectation of success.

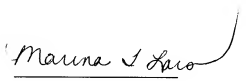
The proper question is not whether an effect on apoptosis is expressly required by the claims, but whether, in the absence of the knowledge of such an effect in the prior art, there can be sufficient predictability to give rise to a reasonable expectation of success. Here, the art was unclear as to whether TRPM-2 encourages or inhibits apoptosis, two opposite results that would have a significant impact on the existence of any therapeutic benefit. Given this lack of clarity, there is no expectation of success.

With respect to the arguments submitted concerning the claims to combination therapy, Applicants apologize for the misstatement concerning the prior experiment, and hereby withdraw those arguments. However, the PC-3 tumor cells do present a valid model for the invention as claimed (including androgen withdrawal) because PC-3 cells lack endogenous androgen receptors and are androgen insensitive. (See attached abstract) Thus, androgen withdrawal is modeled using a non-androgen responsive system. Nevertheless, Applicants have added claims 38 and 39 which expressly recite a method without the androgen withdrawal step.

With respect to claims 12, 13, 16, 17, 29, 30, 33, 38 and 39, Applicants again submit that the specification and the declaration evidence establishes the unexpected synergy that results from the combination of anti-TRPM-2 antisense and chemotherapy agents. The cited references Raghavan and Bruchosky do not show such a combination, and while they show other combinations these teachings do not suggest the synergy. Thus, this is an unexpected results which renders these claims patentable.

For these reasons, Applicants submit that all of the pending claims are now in form for allowance. Favorable reconsideration and allowance of all claims are respectfully urged.

Respectfully submitted,



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